Effects of COVID-19 on Parkinson's disease clinical features: a community-based case-control study

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Abstract

The impact of Coronavirus disease 2019 (COVID-19) on clinical features of Parkinson's disease (PD) has been poorly characterized so far. Out of 141 PD patients resident in Lombardy, we found twelve COVID-19 cases (8.5%), whose mean age and disease duration (65.5 and 6.3 years, respectively) were similar to controls. Changes in clinical features in the period January-April 2020 were compared with those of 36 PD control subjects, matched for sex, age, and disease-duration, using the clinical impression of severity index for PD, the Movement Disorders Society Unified PD Rating Scale parts II and IV, and the non-motor symptoms scale. Motor and nonmotor symptoms significantly worsened in the COVID-19 group, requiring therapy adjustment in one-third of cases. Clinical deterioration was explained by both infection-related mechanisms and impaired pharmacokinetics of dopaminergic therapy. Urinary issues and fatigue were the most prominent nonmotor issues. Cognitive functions were marginally involved, while none experienced autonomic failure.

Introduction

Since the first patient was diagnosed with COVID-19 in Lombardy, on February 20th 2020, Italy has become the third most affected country (>215.000 cases) and 30.000 deaths in the world, as of May 8th, 2020.[1] COVID-19 neurotropic properties may underlie a worsening of chronic neurological diseases, such as Parkinson's disease (PD). COVID-19 may worsen PD by a number of mechanisms,[2-4] including pharmacodynamics changes (*e.g.*, reciprocal interactions between the dopaminergic and renin-angiotensin systems in the substantia nigra and striatum[5]) as well as systemic inflammatory response.[6-9] Patients with PD are frailer than general population because of disease-related factors and age-related co-morbidities.[2-4;10,11] A higher COVID-19 mortality rate has been described in advanced PD patients in association to older age and longer disease duration.[12]

Our primary objective was to investigate the effects of COVID-19 on motor and nonmotor symptoms in a community-based PD cohort. In addition, we explored whether older age and longer disease duration represented risk factors for developing symptomatic COVID-19.

Materials and method

In the present observational, community-based, case-control study, we investigated demographic and clinical features in a cohort of patients with idiopathic PD[13] and COVID-19 as compared to control PD subjects between the pre-outbreak period in Italy (January 01st, 2020) and the end of lockdown restrictions (May 4th, 2020). A 3-month period was chosen to minimize the effect of PD progression on the change in clinical features and the recall bias. Diagnosis of COVID-19 was performed according to clinical and laboratory criteria for probable and confirmed cases, released by the World Health Organization criteria on March 20th, 2020.[14] In symptomatic cases fulfilling criteria for 'probable case'[14,15] we included only patients with close and protracted contacts (*i.e.*, caregivers) with laboratory-confirmed cases.

Out of the 1092 records obtained by searching the Besta Institute clinical software for patients fulfilling the following criteria (i) International Classification of Diseases, Ninth-Revision, Clinical Modification code for parkinsonism 332.0, (ii) resident in the Lombardy region, northern Italy (which is by far the most affected area (>80.000 cases) with the highest case-fatality (>15.000 deaths) in Italy, as of to May 11th, 2020),[16] (ii) visited at least once from January 01st, 2019 to December 31st, 2019, we performed a random selection of 150 PD for subsequent remote interview by a neurologist experienced in movement disorders (by video-consultation or telephone),[2,17,18] which was performed between April 15th and May 4th, 2020. Signed informed consent was obtained prior to remote assessment and collection of clinical data, as approved by the local Ethics Committee.

Out of a total of 141 subjects who accepted to be interviewed, twelve (8.5%) were affected by COVID-19.[14] Compared to overall cohort of 129 PD control subjects (males 56.6%; age 69.1±10.1

years; PD duration 8.2±5.0 years; any comorbidity 62.8%), cases has similar sex distribution (P=0.37), age (P=0.24), PD duration (P=0.20), and co-morbidities (P=0.54). Among those 129 screening negative for COVID-19, a group of 36 PD controls matched for sex, age and disease duration (±1 year) was used for subsequent statistical analysis. A 1:3 ratio was chosen to minimise the effects related to biological variability and the potential presence of asymptomatic COVID-19 among controls.[19] Cases and matched controls underwent in-depth assessment using the following internationally-validated scales. Motor aspects of experiences of daily living and the severity of treatment-related motor complications were assessed using the Movement Disorders Society Unified PD Rating Scale (MDS-UPDRS) parts II and IV, respectively;[20] non-motor symptoms (NMS) were assessed using of the Italian version of the NMS Scale (NMSS);[21] overall changes of motor and nonmotor features was additionally rated using the Clinical Impression of Severity Index for Parkinson's Disease (CISI-PD).[22]

Descriptive statistics were provided for continuous (mean and standard deviation) and categorical (count and percentage) variables, which were compared between groups using the Student's t-test and the Fisher's exact test. Then, between-visit changes in study parameters (January-to-April, 2020) were compared between COVID-19 cases and controls using repeated-measure linear regression models. The role of potential confounders was addressed by MANOVA. All statistical analyses were performed using STATA statistical software release 15.1 (Stata Corporation, College Station, TX) setting the level of significance at a two-tailed P-value <0.05.

Results

Demographic and clinical features at baseline were similar between PD cases and matched control subjects, except for the greater need to increase dopaminergic therapy dosing and higher rate of contacts with confirmed COVID-19 among cases (**Table 1**). COVID-19 symptoms were mild, managed at home without symptomatic therapy in 3 cases (25%); 8 cases (66.7%) had moderate illness, pharmacologically managed at home by the general practitioner; only one patient was hospitalized (8.3%) due to pneumonia. COVID symptoms remitted in ten out of 12 (83.3%) cases and were still ongoing in two patients (16.7%; both remitted at subsequent follow-up on May 15th); nobody died.

At within-group comparison, cases evidenced a significant worsening of the CISI-PD total and motor-signs scores, MDS-UPDRS part-II score, the NMSS total score and the urinary domain sub-score (**Table 2**, footnote d). Between-group case-control analysis additionally revealed greater motor disability (at CISI-PD), motor fluctuations (at MDS-UPDRS part-IV), and nonmotor complaints. Involvement of cognitive functions was marginal (no change at CISI-PD), and autonomic cardiovascular and sexual functions remained unaffected (**Table 2**).

Finally, considering the greater rate of diarrhoea among COVID-19 cases (**Table 1**) and its detrimental effect on the pharmacokinetics of dopaminergic medications (particularly levodopa), we

adjusted a selected subset of models for this symptom and found that worsening of CISI-PD total and motor signs scores was partially mediated by diarrhoea (p=0.002 for both) although COVID-19 status was still a significant contributor (p=0.025 and 0.026, respectively). Worsening of MDS-UPDRS part II and the part IV total score and the NMSS total score were explained by COVID-19 alone (p=0.008, p=0.034, p=0.008, respectively); interestingly, increase in daily OFF-time was fully explained by diarrhoea (p=0.019). We additionally explored whether urinary dysfunction and fatigue were due to COVID-19 or to diminished dopaminergic drive (**Table 2**) and found that urinary problems worsening was due by both motor fluctuations (p<0.001) and COVID-19 (p=0.005), while fatigue was due to COVID-19 alone (p<0.001).

Discussion

To our knowledge, this is the first community-based case-control study describing the effects of symptomatic COVID-19 on PD motor and nonmotor symptoms. First, PD patients who develop symptomatic COVID-19 were neither older age nor with longer disease duration than those screening negative, but rather had nonsignificant 3.5-year younger age and 2.0-year shorter disease duration. The lack of case fatalities is consistent with the Italian case-fatality rate of 3.5% at 60-69 years of age.[15] Similarly, only one patient (8.3%) needed to be admitted to hospital for severe COVID-19 illness, which is in line with the frequency of hospitalization previously reported in general population of the Lombardy region.[23] We expand previous report in advanced PD[12] and show that mild-to-moderate COVID-19 may be contracted independently of age and PD duration and that PD patients with mid-stage PD do not seem to have an overall worse outcome than non-PD population.[15] Concerning the primary objective of the study, we found a worsening of motor and nonmotor symptoms of PD in the COVID-19 group compared to matched control subjects over the study period.

Motor symptoms. COVID-19 induced a significant worsening of motor performance, motor-related disability and experiences of daily living. Worsening of levodopa-responsive motor symptoms and increased daily OFF-time, caused either by the effects of acute systemic inflammatory response[6-9] or by changes in pharmacokinetics, was so pronounced in one-third of cases to prompt neurologists to increase dopaminergic therapy. We explored the relative contribution of suboptimal absorption of oral therapy by adjusting motor endpoints for diarrhoea, which was present in 50% of cases. According to multivariate analysis, concomitant diarrhoea explained the increase in motor fluctuations, but could not entirely explain the worsening of motor disability and motor aspects of experiences of daily living.

Nonmotor symptoms. COVID-19 significant aggravated a number of nonmotor symptoms. Increased fatigue in our cohort was fully explained by COVID-19, confirming that it a common COVID-19 symptom[24], as described in PD following systemic inflammation.[25] Urinary urge/incontinence and nicturia were explained by the infection as well as increased motor fluctuations, which were partly due

to pharmacokinetic issues. COVID-19 was neither a major cause of cognitive dysfunction nor autonomic failure in our cohort of mid-stage PD. Although there was an effect of COVID-19 on attention, it was not severe enough to be detected by CISI-PD. We neither found changes in cardiovascular, gastrointestinal and sexual function domains at the NMSS nor differences in hypotension between the groups.

Strengths and Limitations. The main limitation of this study is the small cohort of COVID-19 patients, albeit statistical analysis could detect several significant changes. There are a number of strengths worth mentioning. First, our case-control study protocol excluded the detrimental effects that quarantine and lockdown restrictions might have played on a number of confounders that influence PD motor and nonmotor symptoms, such as reduced physical activity, enhanced stress, confusion, anxiety, and sleep disturbances.[26] Second, a community-based survey minimised selection bias related to the inclusion of hospitalized patients with severe illness or institutionalised ones with advanced PD and comorbidities, who are more susceptible to neurological manifestations worse outcome.[27,28] Our cohort with mild-to-moderate illness is likely representative of the majority of PD affected by COVID-19, considering that only a minority of cases require hospitalization [29-31]. Third, we excluded secondary and atypical parkinsonisms (including dementia with Lewy bodies), minimising the risk of overestimating either fluctuating or drug-induced worsening of cognitive dysfunction, visual hallucinations, and autonomic failure. Finally, our comprehensive assessment performed by experienced neurologists in a single tertiary referral clinic ensured a homogeneous and standardized approach. Larger multicentre studies would have requested longer time for data collection, increasing patients/caregivers recall bias.

Conclusions

PD patients may experience substantial worsening of motor and nonmotor symptoms during mild-to-moderate COVID-19 illness, independently of age and disease duration. Clinicians should take pharmacokinetic changes into consideration before adjusting therapy regimen (*e.g.*, management of dehydration secondary to fever, diarrhoea, anorexia with reduced water intake). Although we speculate that subacute clinical changes in PD associated to nonsevere COVID-19 illness are likely caused by systemic inflammatory response[8-9] rather than a direct invasion of the central nervous system,[27,28] further studies in larger PD populations are warranted to clarify the cause-effect relationship among clinical changes and the severity of COVID-19 illness, cytokine levels and virus detection in the cerebrospinal fluid.

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Author Roles

(1) Research project: A. Conception, B. Organization, C. Execution; (2) Statistical Analysis: A. Design, B. Execution, C. Review and Critique; (3) Manuscript: A. Writing of the first draft, B. Review and Critique.

RC: 1A, 1B, 1C, 2A, 2B, 3A, 3B; ***SB:*** 1B, 1C, 3B; ***GS:*** 1C, 3B; ***NGA:*** 1C, 3B; ***AEE:*** 1C, 3B; ***LR:*** 1C, 3B; ***GD:*** 1C, 3B; ***EC:*** *2A, 2B, 3B;* ***RE***: 1A, 1B, 3B

References

[1] Coronavirus COVID-19 global cases by the Center for Systems Science and Engineering (CSSE) at Johns Hopkins. Updated May 7, 2020. Accessed May 7, 2020. https://gisanddata.maps.arcgis.com/apps/opsdashboard/index.html#/bda7594740fd40299423467b48e9ecf6

[2] Stoessl AJ, Bhatia KP, Merello M. Editorial: movement disorders in the world of COVID-19. Mov Disord 2020 Apr 6. [Epub ahead of print].

[3] Papa SM, Brundin P, Fung VSC, et al; and the MDS-Scientific Issues Committee. Impact of the COVID-19 Pandemic on Parkinson's Disease and Movement Disorders. Mov Disord. 2020 Apr 6. [Epub ahead of print]

[4] Helmich RC, Bloem BR. The impact of the COVID-19 pandemic on Parkinson's disease: hidden sorrows and emerging opportunities. J Parkinsons Dis 2020; 10(2):351–354.

[5] Labandeira-Garcia JL, Rodriguez-Pallares J, Dominguez-Meijide A, Valenzuela R, Villar-Cheda B, Rodríguez-Perez AI. Dopamine-angiotensin interactions in the basal ganglia and their relevance for Parkinson's disease. Mov Disord 2013; 28(10):1337-42.

[6] Lindqvist D, Kaufman E, Brundin L, Hall S, Surova Y, Hansson O. Non-motor symptoms in patients with Parkinson's disease - correlations with inflammatory cytokines in serum. PLoS One 2012; 7(10):e47387.

[7] Green HF, Khosousi S, Svenningsson P. Plasma IL-6 and IL-17A Correlate with Severity of Motor and Non-Motor Symptoms in Parkinson's Disease. J Parkinsons Dis 2019; 9(4):705-709.

[8] Brugger F, Erro R, Balint B, Kägi G, Barone P, Bhatia KP. Why is there motor deterioration in Parkinson's disease during systemic infections-a hypothetical view. NPJ Parkinsons Dis 2015; 1:15014.

[9] Umemura A, Oeda T, Tomita S, Hayashi R, Kohsaka M, Park K, Sugiyama H, Sawada H. Delirium and high fever are associated with subacute motor deterioration in Parkinson disease: a nested case-control study. PLoS One. 2014; 9(6):e94944.

[10] Vijayan S, Singh B, Ghosh S, Stell R, Mastaglia FL. Brainstem ventilator dysfunction: A plausible mechanism for dyspnea in Parkinson's Disease? Mov Disord. 2020; 35(3):379-388.

[11] Titova N, Qamar MA, Chaudhuri KR. The Nonmotor Features of Parkinson's Disease. Int Rev Neurobiol 2017; 132:33-54.

[12] Antonini A, Leta V, Teo J, Chaudhuri KR. Outcome of Parkinson's Disease patients affected by COVID-19. Mov Disord 2020 Apr 29. [Epub ahead of print]

[13] Postuma RB, Berg D, Stern M, Poewe W, Olanow CW, Oertel W, et al. MDS Clinical Diagnostic Criteria for Parkinson's Disease. Mov Disord 2015; 30: 1591-1600.

[14] World Health Organization. (2020). Global surveillance for COVID-19 caused by human infection with COVID-19 virus: interim guidance, 20 March 2020. Accessed May 8, 2020. World Health Organization. https://apps.who.int/iris/handle/10665/331506.

[15] Onder G, Rezza G, Brusaferro S. Case-Fatality Rate and Characteristics of Patients Dying in Relation to COVID-19 in Italy. JAMA Neurology 2020; 323(18):1775-1776.

[16] Civile DdP. COVID-19 Italia - Monitoraggio della situazione [online]. Available at: http://opendatadpc.maps.arcgis.com/apps/opsdashboard/index.html#/b0c68bce2cce478eaac82fe38d4138b1. Accessed May 12, 2020.

[17] Gabbrielli F, Bertinato L, De Filippis G, Bonomini M, Cipolla M. Istituto Superiore di Sanità. Interim provisions on telemedicine healthcare services during COVID-19 health emergency. Version of April 13, 2020. 2020, ii, 29 p. Rapporti ISS COVID-19 n. 12/2020

[18] Bloem BR, Dorsey ER, Okun MS. The Coronavirus Disease 2019 Crisis as Catalyst for Telemedicine for Chronic Neurological Disorders. JAMA Neurol. 2020 Apr 24. [Epub ahead of print]

[19] Nishiura H, Kobayashi T, Miyama T, Suzuki A, Jung SM, Hayashi K, Kinoshita R, Yang Y, Yuan B, Akhmetzhanov AR, Linton NM. Estimation of the asymptomatic ratio of novel coronavirus infections (COVID-19). Int J Infect Dis. 2020; 94:154-155.

[20] Goetz CG, Tilley BC, Shaftman S, et al. Movement Disorder Society UPDRS Revision Task Force. Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS): scale presentation and clinimetric testing results. Mov Disord 2008; 23:2129–2170.

[21] Cova I, Di Battista ME, Vanacore N, et al. Validation of the Italian version of the Non Motor Symptoms Scale for Parkinson's disease. Parkinsonism Relat Disord 2017; 34:38-42.

[22] Martínez-Martín P, Forjaz MJ, Cubo E, Frades B, de Pedro Cuesta J; ELEP Project Members. Global versus factor-related impression of severity in Parkinson's disease: a new clinimetric index (CISI-PD). Mov Disord 2006; 21(2):208-14.

[23] Grasselli G, Zangrillo A, Zanella A, et al. Baseline Characteristics and Outcomes of 1591 Patients Infected With SARS-CoV-2 Admitted to ICUs of the Lombardy Region, Italy. JAMA. 2020 Apr 6. [Epub ahead of print]

[24] Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020; 395(10223):497-506.

[25] Felger JC, Miller AH. Cytokine effects on the basal ganglia and dopamine function: the subcortical source of inflammatory malaise. Front Neuroendocrinol 2012; 33(3):315-27.

[26] Brooks SK, Webster RK, Smith LE, et al. The psychological impact of quarantine and how to reduce it: rapid review of the evidence. Lancet 2020; 395(10227):912-920.

[27] Mao L, Jin H, Wang M, Hu Y, Chen S, He Q, Chang J, Hong C, Zhou Y, Wang D, Miao X, Li Y, Hu B. Neurologic Manifestations of Hospitalized Patients With Coronavirus Disease 2019 in Wuhan, China. JAMA Neurol. 2020 Apr 10. [Epub ahead of print]

[28] Asadi-Pooya AA, Simani L. Central nervous system manifestations of COVID-19: A systematic review. J Neurol Sci 2020 Apr 11; 413:116832.

[29] Bi Q, Wu Y, Mei S, et al. Epidemiology and transmission of COVID-19 in 391 cases and 1286 of their close contacts in Shenzhen, China: a retrospective cohort study [published online ahead of print, 2020 Apr 27]. Lancet Infect Dis 2020; S1473-3099(20)30287-5.

[30] Lechien JR, Chiesa-Estomba CM, Place S, et al. Clinical and Epidemiological Characteristics of 1,420 European Patients with mild-to-moderate Coronavirus Disease 2019. J Intern Med. 2020;10.1111/joim.13089 Apr 30 [Epub ahead of print].

[31] Kim GU, Kim MJ, Ra SH, et al. Clinical characteristics of asymptomatic and symptomatic patients with mild COVID-19. Clin Microbiol Infect. 2020; S1198-743X(20)30268-8. Apr 30 [Epub ahead of print]

Table 1. Characteristics of the study population.

Variable	Cases (N = 12)	Controls (N = 36)	P-value[f]
General features			
Male gender, N (%)	5 (41.7)	15 (41.7)	1.00
Age, years [Mean (SD)]	65.5 (8.9)	66.3 (8.1)	0.78
Current Smoking, N (%)	0 (0.0)	3 (8.3)	0.56
Past Smoking, N (%)	5 (41.7)	10 (27.8)	0.48
Frequency of smoking, N cigarettes/day (%)	10.0 (8.7)	9.1 (7.3)	0.82
Body mass index, kg/m^2 [Mean (SD)]	25.1 (3.8)	25.5 (3.8)	0.77
Body weight, kg [Mean (SD)]	67.0 (11.5)	71.3 (14.5)	0.36
Seasonal vaccinations in 2019, total N (%)	3 (25.0)	9 (25.0)	1.00
of whom, **Anti-H1N1**, N (%)	3 (25.0)	9 (25.0)	1.00
Anti-Pneumococcus, N (%)	1 (8.3)	2 (5.5)	1.00
PD-related features [a]			
Age at PD onset, years [Mean (SD)]	59.0 (8.1)	60.4 (7.8)	0.58
Tremor-dominant phenotype, N (%)	6 (50)	18 (50)	1.00
Disease duration, years [Mean (SD)]	6.3 (3.6)	6.1 (2.9)	0.79
Hoehn-Yahr stage, Mean (SD)	1.8 (0.7)	1.8 (0.6)	0.95
Dementia, N (%)	0 (0.0)	3 (8.3)	0.56
Therapy			
Levodopa, N (%)	10 (83.3)	28 (77.8)	1.00
Levodopa dose, mg/day [Mean (SD)]	400.0 (119.3)	433.6 (227.1)	0.09
DA, N (%)	9 (75.0)	23 (63.9)	0.73
iMAO-B, N (%)	6 (50.0)	16 (44.4)	0.75
iCOMT, N (%)	0 (0.0)	4 (11.1)	0.56
Amantadine, N (%)	0 (0.0)	0 (0.0)	1.00
Advanced-stage Invasive Therapies, N (%) [b]	1 (8.3)	1 (2.8)	0.44
Total LEDD, mg/day [Mean (SD)]	571 (517)	487 (327)	0.52
Therapy adjustment during the study period, N (%)	4 (33.3)	2 (5.5)	**0.028**
Risk factors for COVID-19			
Contact with confirmed or suspect COVID-19, total N (%) [c]	8 (66.7)	4 (11.1)	**<0.001**
of whom, **Confirmed COVID-19**, N (%)	6 (50.0)	0 (0.0)	**<0.001**

Suspect COVID-19, N (%)	2 (16.7)	4 (11.1)	0.63
Comorbidities			
Any	9 (75)	24 (66.7)	0.73
COPD	1 (8.3)	4 (11.1)	1.00
Hypertension, N (%)	4 (33.3)	16 (44.4)	0.74
Obesity, N (%)	1 (8.3)	2 (5.5)	1.00
Diabetes mellitus, N (%)	0 (0.0)	2 (5.5)	1.00
Cardiopathy, N (%)	1 (8.3)	5 (13.9)	1.00
Malignancies, N (%)	2 (16.7)	3 (8.3)	0.59
Immune system diseases, N (%)	1 (8.3)	1 (2.8)	1.00
Immune-modulating therapies, N (%) [d]	2 (16.7)	2 (5.5)	0.26
Renal or Hepatic dysfunction, N (%)	1 (8.3)	5 (13.9)	1.00
Other neurological diseases, N (%) [e]	1 (8.3)	4 (11.1)	1.00
COVID-19 symptoms			
Fever, N (%)	10 (83.3)	2 (5.5)	**<0.001**
Cough, N (%)	9 (75%)	3 (8.3)	**<0.001**
Dyspnea, N (%)	4 (33.3)	0 (0.0)	**0.003**
Dizziness, N (%)	2 (16.6)	1 (2.8)	0.15
Headache, N (%)	4 (33.3)	3 (8.3)	0.055
Anorexia, N (%)	5 (41.6)	1 (2.8)	**0.002**
Diarrhoea, N (%)	6 (50)	2 (5.5)	**0.002**
Fatigue, N (%)	7 (58.4)	3 (8.3)	**<0.001**
Skeletal muscle pain, N (%)	7 (58.4)	2 (5.5)	**<0.001**
Nausea/Vomiting, N (%)	2 (16.6)	1 (2.8)	0.15
Smell loss, N (%)	4 (33.3)	1 (2.8)	**0.011**
Taste loss, N (%)	2 (16.6)	1 (2.8)	0.15
Hypotension, N (%)	2 (16.6)	1 (2.8)	0.15

Abbreviations: **COPD**, Chronic obstructive pulmonary disease, including asthma; **DA**, dopamine agonists; **iCOMT**, catechol-O-methyltransferase inhibitors; **ICU**, intensive care unit; **iMAO-B**, Monoamine Oxidase type B Inhibitors; **LEDD**, levodopa equivalent daily dose; **PD**, Parkinson's disease; **Pts**, patients.
Data are shown as number of patients (N) and frequency (%) or as mean (standard deviation).
[a] These data refer to the baseline state (January 2020) before the COVID outbreak in Italy
[b] One case was on Levodopa/Carbidopa gel infusion; one control was on subthalamic nucleus stimulation.
[c] Defined according to the WHO criteria.[14]
[d] Including daily intake of drugs targeting rheumatic diseases or malignancies (e.g., steroids, hydroxychloroquine, methotrexate, azathioprine, etc.) prior to the baseline assessment.
[e] One patient with meningioma among cases, 4 patients with chronic cerebrovascular disease among controls.
[f] Between-group comparisons of continuous variables were performed using the unpaired Student's t-test, while categorical variables were analyzed by the Fisher's exact test.

Table 2. Analysis of study endpoints (CISI-PD, MDS-UPDRS, NMSS).

	Cases (N = 12)			Controls (N = 36)			Statistics	
Variable	**Baseline** [a]	**End of study** [a]	**Change** [b]	**Baseline** [a]	**End of study** [a]	**Change** [b]	**Between-group difference in change** [b,c]	**P-value** [c]
a) CISI-PD								
Total score	6.2 (4.1)	7.4 (4.1)	1.3 (0.3, 2.2) [d]	7.5 (4.7)	7.6 (4.8)	0.1 (0.0, 0.2)	1.2 (0.6, 1.7)	**<0.001**
Motor signs	2.3 (1.4)	3.0 (1.3)	0.7 (0.2, 1.2) [d]	2.7 (1.4)	2.7 (1.4)	0.0 (-0.0, 0.1)	0.6 (0.3, 0.9)	**<0.001**
Disability	2.1 (1.1)	2.4 (1.4)	0.3 (-0.1, 0.7)	2.4 (1.4)	2.4 (1.4)	0.0 (0.0, 0.0)	0.3 (0.1, 0.5)	**0.003**
Motor complications	0.6 (1.2)	0.7 (1.4)	0.1 (-0.1, 0.3)	1.0 (1.4)	1.0 (1.4)	0.0 (-0.1, 0.1)	0.1 (-0.1, 0.2)	0.42
Cognitive status	1.2 (1.2)	1.3 (1.2)	0.1 (-0.1, 0.4)	1.5 (1.5)	1.5 (1.5)	0.0 (-0.1, 0.1)	0.1 (-0.0, 0.3)	0.089
b) MDS-UPDRS								
UPDRS part II	11.9 (7.6)	13.7 (9.4)	1.8 (0.4, 3.1) [d]	12.0 (8.3)	12.2 (8.3)	0.2 (0.0, 0.4) [d]	1.6 (0.8, 2.3)	**<0.001**
UPDRS part IV	3.0 (6.2)	4.2 (8.1)	1.2 (-0.2, 2.5)	4.8 (6.6)	4.8 (6.6)	0.0 (0.0, 0.0)	1.2 (0.5, 2.9)	**0.002**
UPDRS part IV - OFF [e]	1.1 (2.0)	1.5 (2.8)	0.4 (-0.2, 1.0)	1.7 (2.5)	1.7 (2.5)	0.0 (0.0, 0.0)	0.4 (0.1, 0.7)	**0.014**
UPDRS part IV – DYSK [e]	0.3 (1.2)	0.5 (1.7)	0.2 (-0.2, 0.5)	0.6 (1.2)	0.6 (1.2)	0.0 (0.0, 0.0)	0.2 (-0.0, 0.4)	0.083
c) NMSS								
Total score	39.3 (28.1)	49.7 (43.1)	10.4 (0.2, 20.6) [d]	41.9 (40.8)	41.8 (41.1)	-0.1 (-0.7, 0.5)	10.5 (5.2, 15.9)	**<0.001**
Cardiovascular	1.5 (1.3)	1.8 (3.3)	0.3 (-1.1, 1.6)	1.3 (2.3)	0.9 (1.9)	-0.4 (-0.6, -0.2) [d]	0.6 (-0.2, 1.4)	0.13
Sleep/Fatigue	8.3 (6.4)	10.5 (7.1)	2.2 (-0.2, 4.6)	10.0 (9.7)	9.8 (9.7)	-0.1 (-0.4, 0.1)	2.3 (1.0, 3.6)	**0.001**
Mood/Apathy	8.6 (14.3)	11.8 (17.9)	3.2 (-1.2, 7.5)	7.6 (11.0)	7.6 (11.3)	0.0 (-0.4, 0.4)	3.1 (0.8, 5.5)	**0.010**
Perceptual problems	0.9 (1.6)	0.9 (1.6)	0.0 (0.0, 0.0)	0.7 (1.6)	0.7 (1.6)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	1.00
Attention/memory	3.2 (4.1)	4.7 (7.8)	1.5 (-1.1, 4.1)	4.9 (7.1)	4.9 (7.1)	0.0 (-0.1, 0.2)	1.4 (0.1, 2.8)	**0.038**
Gastrointestinal [f]	3.3 (5.1)	3.2 (5.2)	-0.1 (-0.8, 0.5)	3.0 (3.8)	3.2 (3.9)	0.2 (-0.0, 0.4)	-0.4 (-0.9, 0.2)	0.17
Urinary	8.6 (7.5)	10.8 (9.3)	2.2 (0.1, 4.4) [d]	8.3 (9.0)	8.3 (9.0)	0.0 (0.0, 0.0)	2.3 (1.1, 3.4)	**<0.001**
Sexual function	1.3 (2.0)	1.3 (2.0)	0.0 (0.0, 0.0)	2.1 (4.5)	2.1 (4.5)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	1.00
Miscellaneous	3.5 (3.3)	4.8 (3.7)	1.3 (-0.5, 3.0)	4.2 (5.9)	4.3 (5.9)	0.1 (-0.0, 0.2)	1.2 (0.2, 2.1)	**0.014**

Abbreviations: **CISI-PD,** Clinical Impression of Severity Index for Parkinson's Disease. **MDS-UPDRS**, Movement Disorders Society Unified PD Rating Scale; **NMSS**, non-motor symptoms scale.

[a] Data are provided as mean (standard deviation)

[b] Data are provided as mean (95% confidence interval)
[c] According to repeated-measures linear regression model
[d] Significantly different compared to baseline (test for within-group comparison)
[e] OFF-related subscore was calculated as the sum of items 4.3, 4.4, 4.5. Dyskinesias subscore was calculated as the sum of items 4.1, 4.2
[f] Note that the gastrointestinal domain of the NMSS does not include assessment of diarrhoea.